PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

SANZO, Michael, A.
Vinson & Elkins
2300 First City Tower
1001 Fannin
Houston, TX 77002-6760
ÉTATS-UNIS D'AMÉRIQUE

RECEIVED
OCT 27 1998
Docket Sec.
Vinson & Elkins

Date of mailing (day/month/year) 20 October 1998 (20.10.98)	
Applicant's or agent's file reference NOV550/58000	**IMPORTANT NOTIFICATION**
International application No. PCT/US98/18284 4-1(A)	International filing date (day/month/year) 03 September 1998 (03.09.98)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 04 September 1997 (04.09.97)
Applicant NOVONEURON, INC. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
04 Sept 1997 (04.09.97)	60/057,921	US	19 Octo 1998 (19.10.98)

Th International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

S. Mafla

Telephone No. (41-22) 338.83.38

002292088

Form PCT/IB/304 (July 1998)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

SANZO, Michael, A.
Vinson & Elkins
2300 First City Tower
1001 Fannin
Houston, TX 77002-6760
ÉTATS-UNIS D'AMÉRIQUE

RECEIVED
OCT 31 1998
Docket Sec.
Vinson & Elkins

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
09 October 1998 (09.10.98)	
Applicant's or agent's file reference NOV550/58000 4-1(A)	**International application No.** PCT/US98/18284

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

NOVONEURON, INC. (for all designated States except US)
MASH, Deborah, C. (for US)

International filing date	:	03 September 1998 (03.09.98)
Priority date(s) claimed	:	04 September 1997 (04.09.97)
Date of receipt of the record copy by the International Bureau	:	08 October 1998 (08.10.98)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,SD,SZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CU,CZ,DE,DK,EE,ES,FI,GB,GE,GH,GM, HR,HU,ID,IL,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,PL, PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,US,UZ,VN,YU,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [ ] confirmation of precautionary designations
- [X] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

J. Leitao

Telephone No. (41-22) 338.83.38

002276285

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

eceiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* NOV550/58000

Box No. I TITLE OF INVENTION

NORIBOGAINE IN THE TREATMENT OF PAIN AND DRUG ADDICTION

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

NovoNeuron, Inc.
1 Northeast 19th Street
Suite 399
Miami, Florida 33132
US

☐ This person is also inventor.

Telephone No.
(305) 243-5888

Facsimile No.
(305) 243-3649

Teleprinter No.

State *(that is, country)* of nationality:
US

State *(that is, country)* of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Mash, Deborah C.
7552 W. Treasure Drive
North Bay Village, Florida 33141
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
US

State *(that is, country)* of residence:
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Sanzo, Michael A.
Vinson & Elkins
2300 First City Tower
1001 Fannin
Houston, Texas 77002-6760
US

Telephone No.
(202) 639-6585

Facsimile No.
(202) 639-6604

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box N .V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked):*

Regional Patent

☒ **AP ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line):*

☒ **AL** Albania .....
☒ **AM** Armenia .....
☒ **AT** Austria .....
☒ **AU** Australia .....
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina .....
☒ **BB** Barbados
☒ **BG** Bulgaria .....
☒ **BR** Brazil .....
☒ **BY** Belarus
☒ **CA** Canada
☒ **CH and LI** Switzerland and Liechtenstein
☒ **CN** China .....
☒ **CU** Cuba .....
☒ **CZ** Czech Republic .....
☒ **DE** Germany .....
☒ **DK** Denmark .....
☒ **EE** Estonia .....
☒ **ES** Spain .....
☒ **FI** Finland .....
☒ **GB** United Kingdom
☒ **GE** Georgia .....
☒ **GH** Ghana .....
☒ **GM** Gambia
☒ **GW** Guinea-Bissau .....
☒ **HR** Croatia
☒ **HU** Hungary .....
☒ **ID** Indonesia
☒ **IL** Israel .....
☒ **IS** Iceland
☒ **JP** Japan .....
☒ **KE** Kenya .....
☒ **KG** Kyrgyzstan .....
☒ **KP** Democratic People's Republic of Korea .....
☒ **KR** Republic of Korea .....
☒ **KZ** Kazakhstan .....
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho .....
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MD** Republic of Moldova .....
☒ **MG** Madagascar .....
☒ **MK** The former Yugoslav Republic of Macedonia .....
☒ **MN** Mongolia
☒ **MW** Malawi .....
☒ **MX** Mexico .....
☒ **NO** Norway
☒ **NZ** New Zealand .....
☒ **PL** Poland .....
☒ **PT** Portugal .....
☒ **RO** Romania
☒ **RU** Russian Federation .....
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia .....
☒ **SK** Slovakia .....
☒ **SL** Sierra Leone
☒ **TJ** Tajikistan .....
☒ **TM** Turkmenistan .....
☒ **TR** Turkey .....
☒ **TT** Trinidad and Tobago .....
☒ **UA** Ukraine .....
☒ **UG** Uganda .....
☒ **US** United States of America .....
☒ **UZ** Uzbekistan .....
☒ **VN** Viet Nam .....
☒ **YU** Yugoslavia .....
☒ **ZW** Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

☒ Guatemala .....
☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) (04.09.97) 4 September 1997	60/057,921	US		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): 1

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA/ EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country (or regional Office)

Box No. VIII CHECK LIST: LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	:	3
description (excluding) sequence listing part)	:	10
claims	:	3
abstract	:	1
drawings	:	1
sequence listing part of description	:	
Total number of sheets	:	18

This international application is **accompanied** by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as items(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify):*

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Michael A. Sanzo

Michael A. Sanzo

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT
GENERAL POWER OF ATTORNEY
(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

NovoNeuron, Inc.
1 Northeast 19th Street, Suite 399
Miami, Florida 33132
US

hereby appoint(s) the following person(s) as: ☒ agents ☐ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Armitage, Robert A.; and Sanzo, Michael A., both members of the Firm of:

Vinson & Elkins L.L.P.
2300 First City Tower
1001 Fannin
Houston, Texas 77002-6760

to represent the undersigned before:

☒ all the competent International Authorities
☐ the International Searching Authority only
☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the United States Patent Office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several persons, each of them must sign; beneath each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power)*:

For: NovoNeuron, Inc.

By: W. Lee Hearn

Signature: W. Lee Hearn

Title: President

Date: 08/31/98

PCT
GENERAL POWER OF ATTORNEY
(for several international applications filed under the Patent Cooperation Treaty)

(PCT Rule 90.5)

The undersigned person(s):
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Deborah C. Mash
7552 W. Treasure Drive
North Bay Village, Florida 33141
US

hereby appoint(s) the following person(s) as: ☒ agents ☐ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Armitage, Robert A.; and Sanzo, Michael A., both members of the Firm of:

Vinson & Elkins L.L.P.
2300 First City Tower
1001 Fannin
Houston, Texas 77002-6760

to represent the undersigned before:

☒ all the competent International Authorities
☐ the International Searching Authority only
☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the United States Patent Office as receiving Office and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several persons, each of them must sign; beneath each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power)*:

Signature: Deborah C. Mash, Ph. D.

Name: Deborah C. Mash

Date: 09/02/98

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: **NOV550/58000**

Applicant: **NovoNeuron, Inc.**

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 240.00 T

2. SEARCH FEE . . . . . 1,250.00 S

International search to be carried out by **EP**

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains **18** sheets.

first 30 sheets . . . . . 455.00 b_1

0 remaining sheets x **$0.00** additional amount = 0.00 b_2

Add amounts entered at b_1 and b_2 and enter total at B . . 455.00 B

Designation Fees

The international application contains **77** designations.

11 number of designation fees payable *(maximum 11)* x **105.00** amount of designation fee = 1,155.00 D

Add amounts entered at B and D and enter total at I . . . . . 1,610.00 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . 15.00 P

5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P, and enter total in the TOTAL box: **3,115.00** TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

- ☐ authorization to charge deposit account (see below)
- ☒ cheque
- ☐ postal money order
- ☐ bank draft
- ☐ cash
- ☐ revenue stamps
- ☐ coupons
- ☐ other *(specify)*:

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ **US**

- ☐ is hereby authorized to charge the total fees indicated above to my deposit account.
- ☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- ☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

22-0365 Deposit Account Number

September 3, 1998 Date *(day/month/year)*

Michael A. Sanz Signature

See Notes to the fee calculation sheet

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:

MICHAEL A. SANZO
VINSON & ELKINS
2300 FIRST CITY TOWER
1001 FANNIN
HOUSTON, TX 77002-6760

RECEIVED
OCT 08 1998
Docket Sec.
Vinson & Elkins

NOTIFICATION CONCERNING PAYMENT OF PRESCRIBED FEES

(PCT Rules 14, 15 and 16 and Administrative Instructions, Section 323(d))

Date of mailing (*day/month/year*)	05 OCT 1998
Applicant's or agent's file reference: NOV550/58000	**PAYMENT DUE** See item 3 for time limits

International application No.	International filing date/Date of receipt (*day/month/year*)	Priority date (*day/month/year*)
PCT/US98/18284	03 SEP 98	04 SEP 97

Applicant: NOVONEURON, INC.

1. The applicant is hereby notified that this receiving Office has received:

☑ **the payment** of all the prescribed fees, and ☐ **an overpayment**, which will be refunded in due course.

☐ **no or insufficient payment** of the prescribed fees and the applicant is hereby **invited to pay the balance due**, as summarized under item 2, within the time limit(s) indicated under item 3.

2. **Fees and payment calculation:**

Total fees payable	− Amount paid	= Balance
_____	_____	_____

☐ The details of the calculation are given in the Annex.

3. **Time limit(s) for payment of prescribed fees:**

☐ within ONE MONTH from the date of receipt of the international application (for the transmittal fee (if any), the search fee, the basic fee and the designation fee)

☐ within 12 MONTHS from the priority date (only for the designation fee and only if this time limit expires later than the above time limit)

☐ within 16 MONTHS from the priority date (only for the fee for priority document). The applicant's attention is drawn to the fact the request made by the applicant under Rule 17.1(b) will be considered not to have been made unless the fee is paid within that time limit.

4. Additional observations *(if necessary)*:

☐ The search copy will not be transmitted to the International Searching Authority until the search fee is paid (therefore the start of the international search will be delayed).

☐ Other *(specify)*:

Name and mailing address of the receiving Office	Authorized officer
Assistant Commissioner for Patents Box PCT Washington, D.C. 20231 Attn: RO/US	JERYL McDOWELL
Facsimile No.	Telephone No. 703-305-3939

Form PCT/RO/102 (July 1992; reprint January 1996)

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No. PCT/US 98/18284

(03.09.98) 03 SEP 1998

Date stamp of the receiving Office

Applicant's or agent's file reference: **NOV550/58000**

Applicant: **NovoNeuron, Inc.**

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE	240.00 T	240
2. SEARCH FEE	1,250.00 S	1250

International search to be carried out by **EP**

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains **18** sheets.

first 30 sheets	455.00 b_1	455
0 remaining sheets x **$0.00** additional amount =	0.00 b_2	—
Add amounts entered at b_1 and b_2 and enter total at B	455.00 B	455

Designation Fees

The international application contains **77** designations.

11 number of designation fees payable *(maximum 11)*	x	**105.00** amount of designation fee	= 1,155.00 D	1155

Add amounts entered at B and D and enter total at I	1,610.00 I	1610

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and

4. FEE FOR PRIORITY DOCUMENT *(if applicable)*	15.00 P	15
5. TOTAL FEES PAYABLE Add amounts entered at T, S, I and P, and enter total in the TOTAL box	3,115.00 TOTAL	3115

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below)	☐ bank draft	☐ coupons
☒ cheque	☐ cash	☐ other *(specify)*:
☐ postal money order	☐ revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ **US**

☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

22-0365	September 3, 1998	Michael A. Sanz
Deposit Account Number	Date *(day/month/year)*	Signature

See Notes to the fee calculation sheet

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

To:

MICHAEL A. SANZO
VINSON & ELKINS
2300 FIRST CITY TOWER
1001 FANNIN
HOUSTON, TX 77002-6760

PCT

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing (*day/month/year*): 05 OCT 1998

Applicant's or agent's file reference: NOV550/58000

IMPORTANT NOTIFICATION

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US98/18284	03 SEP 98	04 SEP 97

Applicant: NOVONEURON, INC.

Title of the invention: NORIBOGAINE IN THE TREATMENT OF PAIN AND DRUG ADDICTION

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

- [x] was transmitted to the International Bureau on 05 OCT 1998
- [ ] has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:
  - [ ] because the necessary national security clearance has not yet been obtained.
  - [ ] because (*reason to be specified*):

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

3. FOREIGN TRANSMITTAL LICENSE INFORMATION — Completed by: D. Hill

- [ ] Additional license for foreign transmittal not required. This subject matter is covered by a license already granted on the equivalent U.S. national application. Refer to that license for information concerning its scope.
- [ ] License for foreign transmittal not required. 37 CFR 5.11(e)(1) or 37 CFR 5.11(e)(2). However, a license may be required for additional subject matter. See 37 CFR 5.15(b).
- [x] Foreign transmittal license granted. 35 U.S.C. 184; 37 CFR 5.11 on 9-16-98 (date):
  - [x] 37 CFR 5.15(a)
  - [ ] 37 CFR 5.15(b)

Name and mailing address of the receiving Office
Assistant Commissioner for Patents
Box PCT
Washington, D.C. 20231
Attn: RO/US

Facsimile No.

Authorized officer
JMM
JERYL McDOWELL
703-305-3430

Telephone No.

Form PCT/RO/105 (July 1992)

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:

MICHAEL A. SANZO
VINSON & ELKINS
2300 FIRST CITY TOWER
1001 FANNIN
HOUSTON, TX 77002-6760

INVITATION TO CORRECT DEFECTS IN THE INTERNATIONAL APPLICATION

(PCT Articles 3(4)(i) and 14(1) and Rule 26)

Applicant's or agent's file reference: NOV550/58000	Date of mailing (*day/month/year*): 05 OCT 1998
International application No.: PCT/US98/18284	**REPLY DUE** within **ONE MONTH** from the above date of mailing
Applicant: NOVONEURON, INC.	International filing date (*day/month/year*): 03 SEP 98

The applicant is hereby invited, within the time limit indicated above, to correct the defects in the international application, which are specified on the attached

☐ Annex A ☐ Annex B ☑ Annex C

Additional observations (if necessary):

HOW TO CORRECT THE DEFECTS?

Correction must be submitted by filing a replacement sheet embodying the correction and a letter accompanying the replacement sheet, which shall draw attention to the difference between the replaced sheet and the replacement sheet. A correction may be stated in a letter only if it is of such a nature that it can be transferred from the letter to the record copy without adversely affecting the clarity and direct reproducibility of the sheet onto which the correction is to be transferred (Rule 26.4(a)).

ATTENTION

Failure to correct the defects will result in the international application being considered withdrawn by this receiving Office (see Rule 26.5 for further details).

A copy of this invitation and any attachments has been sent to the International Bureau

☑ and the International Searching Authority.

Name and mailing address of the receiving Office Assistant Commissioner for Patents Box PCT Washington, D.C. 20231 Attn: RO/US	Authorized officer JERYL McDOWELL
Facsimile No.	Telephone No. 703-305-3639

Form PCT/RO/106 (July 1992)

The receiving Office has found that, with regard to the presentation of the **drawings of the international application as filed,** the physical requirements are not complied with to the extent that compliance therewith is necessary for:

1. ☐ reasonally uniform international publication (Rules 11 and 26.3(a)(i)) *(defects to be specified)*:

Sheets containing drawings:

a. ☐ the sheets do not admit of direct reproduction.
b. ☐ the sheets are not free from creases, cracks, folds.
c. ☐ one side of the sheets is not left unused.
d. ☐ the paper of the sheets is not flexible/strong/white/smooth/non-shiny/durable.
e. ☐ the drawings do not commence on a new sheet.
f. ☐ the sheets are not connected as prescribed (Rule 11.4(b)).
g. ☐ the sheets are not A4 size (29.7cm x 21cm).
h. ☐ the minimum margins on the sheets are not as prescribed (top: 2.5cm; left side: 2.5cm; right side: 1.5cm; bottom: 1cm).
i. ☐ the file reference number indicated on the sheets does not appear in the left-hand corner of the sheets, within 1.5cm of the top of the sheets.
j. ☐ the file reference number exceeds the maximum of 12 characters.
k. ☐ the sheets are not free from frames around usable or used surfacts.
l. ☐ the sheets are not numbered in consecutive Arabic numerals (e.g. 1/3, 2/3, 3/3).
m. ☐ the sheet numbers are not centered at the top or bottom of the sheets.
n. ☐ the sheet numbers are in the margin (see h. above for the size of the margins).
o. ☐ the sheets contain alterations/overwritings/interlineations/too many erasures.
p. ☐ the sheets contain photocopy marks.

Drawings (Rule 11.13):

a. ☐ do not admit of direct reproduction.
b. ☐ contain unnecessary text matter.
c. ☐ contain words so placed as to prevent translation without interference with lines thereof.
d. ☐ are not executed in durable black color; the lines are not uniformly thick and well-defined.
e. ☐ contain cross-sections not properly hatched.
f. ☐ would not be properly distinguishable in reduced reproduction.
g. ☐ contain scales not represented graphically.
h. ☐ contain numbers, letters and reference lines lacking simplicity and clarity.
i. ☐ contain lines drafted without the aid of drafting instruments.
j. ☐ contain disproportionate elements of a figure not necessary for clarity.
k. ☐ contain numbers and letters of height less than 0.32 cm.
l. ☐ contain letters not conforming to the Latin, and where customary, Greek alphabets.
m. ☐ contain figures on two or more sheets which form a single complete figure but which are not able to be assembled without concealing parts thereof.
n. ☐ contain figures which are not properly arranged and clearly separated.
o. ☐ contain different figures not numbered in consecutive Arabic numerals.
p. ☐ contain different figures not numbered independent of the numbering of the sheets.
q. ☐ are not restricted to reference signs mentioned in the description.
r. ☐ do not contain reference signs that are mentioned in the description.
s. ☐ contain the same feature denoted by different reference signs.
t. ☑ are not arranged in an upright position, clearly separated from one another. fig 1
u. ☐ are not presented sideways with the top of the figures at the left side of the sheets.

2. ☐ satisfactory reproduction (Rules 11 and 26.3(b)(i)).

Further observations (if neccesary):

New drg fig 1

Form PCT/RO/106 (Annex C1) (July 1998)

Lamont Hunter
PCT International Division
(703) 305-3686

'TENT COOPERATION TRE TY

From the RECEIVING OFFICE

PCT

To:

MICHAEL A. SANZO
VINSON & ELKINS
2300 FIRST CITY TOWER
1001 FANNIN
HOUSTON, TX 77002-6760

NOTIFICATION REGARDING CERTAIN CORRECTIONS MADE *EX OFFICIO*

(PCT Administrative Instructions, Section 327)

Applicant's or agent's file reference: NOV550/58000	Date of mailing (*day/month/year*): 05 OCT 1998
International application No.: PCT/US98/18284	**REPLY DUE**: NONE. However, see paragraph 3 below
Applicant: NOVONEURON, INC.	International filing date (*day/month/year*): 03 SEP 98

1. The applicant is hereby notified that this receiving Office has corrected formal defects in the international application *ex officio*, as shown on the attached copy of:

- [x] the request, sheet No.: 2
- [ ] the description, sheet No.: _____
- [ ] the claims, sheet No.: _____
- [ ] the drawings, sheet No.: _____
- [ ] other *(specify)*: _____

2. If the applicant agrees with these corrections, no further action is required in this regard.

3. **In case of disagreement** with these corrections, the applicant should promptly inform this receiving Office accordingly.

Name and mailing address of the receiving Office: Assistant Commissioner for Patents, Box PCT, Washington, D.C. 20231, Attn: RO/US	Authorized officer: JMM JERYL McDOWELL
Facsimile No.	Telephone No. 703-305-3630

Form PCT/RO/146 (July 1992)

TO:
MICHAEL A. SANZO
VINSON & ELKINS
2300 FIRST CITY TOWER
1001 FANNIN
HOUSTON,, TX 77002 6760

UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

NOTIFICATION OF STATUS OF REQUIREMENTS UNDER 35 U.S.C. 371

DATE OF MAILING (day/month/year): 05 OCT 98

FILE REFERENCE: NOV550/58000

IDENTIFICATION OF INTERNATIONAL APPLICATION

International application No.	International filing date (day/month/year)	Priority Date Claimed
PCT/US98/18284	03 SEP 98	04 SEP 97

Applicant for DO/EO/US: MASH, DEBORAH C.

NOTIFICATION

The applicant is hereby advised that the U.S. Patent and Trademark Office in its capacity as [X] Designated Office [ ] Elected Office has received following items as of the date of mailing indicated above.

1. [ ] U.S. Nation fee [35 U.S.C 371 (c) (1)]
2. [ ] Oath of declaration [35 U.S.C 371 (c) (4)]
3. [X] Copy of International application as [35 U.S.C 371 (c) (2)]
4. [ ] Translation of Application [35 U.S.C 371 (c) (2)]
5. [ ] Amendments under PCT Article 19 [35 U.S.C 371 (c) (3)]
6. [ ] Translation of PCT Article 19 Amendments [35 U.S.C 371 (c) (3)]
7. [ ] Search Report or Declaration under PCT Article 17(2) [35 U.S.C 371 (a)]
8. [ ] International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3)(b) [35 U.S.C 371 (a)]
9. [ ] Translation of Annexs to the International Preliminary Examination Report under PCT Article 36(3)(b) [35 U.S.C 371 (c) (5)]
10. [ ] Other items received:
    - [ ] Assignment Document
    - [ ] Prior Art Statement
    - [ ] Preliminary Amendment

A. [ ] Requirements for U.S. National processing have been met. Processing will commence
- [ ] at the expiration of the applicable time limit under either
  - [ ] PCT Article 22 [35 U.S.C 371 (b)] or
  - [ ] PCT Article 39 [35 U.S.C 371 (b)]
- [ ] on the date indicated below under the provisions of 35 U.S.C 371 (f)

U.S. NATIONAL SERIAL#	DATE UNDER 35 U.S.C. 102(e)	DATE OF COMMENCEMENT OF NATIONAL PROCESSING

All correspondence submitted after the date of commencement of U.S. National processing indicated above should refer to the U.S. National Serial Number and the appropriate U.S. National processing organization of Officer.

B. [ ] As the above identified application has been accepted for U.S. National processing under the provision of 35 U.S.C.371 (f) before expiration of the applicable time limit under [ ] PCT Article 22 [ ] PCT Article 39, applicant is reminded that
- [ ] Amendments under PCT Article 19 and/or
- [ ] the International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3) (a), and (b) and any translation thereof, if applicable, must be submitted to the Patent and Trademark Office as soon as they are available.

International application No.	International filing date	Priority Date Claimed
PCT/US98/18284	03 SEP 98	04 SEP 97

C. [X] In order that U.S. National processing may begin, certain items must be received by the DO/EO/US by the expiration of applicable time limit under

- [X] PCT Article 22 or
- [ ] PCT Article 39.

Specifically:

- [X] 1. U.S. National Fee
- [X] 2. Oath or Declaration
- [ ] 3. Copy of Application
- [ ] 4. Translation of application
- [ ] 5. Amendments under PCT Article 19, if any
- [ ] 6. Translation of PCT Article 19 Amendments, if applicable
- [ ] 7. Search Report or PCT Article 17(2) declaration
- [ ] 8. International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3)(a), if applicable
- [ ] 9. Translation of Annexs to the International Preliminary Examination Report under PCT Article 36(3)(b), if appliable

THE ABOVE CHECK ITEMS MUST BE TIMELY RECEIVED TO AVOID ABANDONMENT OF THE APPLICATION. [35. U.S.C. 371(d)]

D. Further information for the applicant:

This is only a reminder.

UNITED STATES DESIGNATED/ELECTED OFFICE

Address Only:
Assistant Commissioner for Patent
Box PCT
Washington, D.C. 20231 Attn:RO/US

Authorized Office
Jeryl McDowell

TAUS98/18284

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AL Albania .....
☒ AM Armenia .....
☒ AT Austria .....
☒ AU Australia .....
☒ AZ Azerbaijan
☒ BA Bosnia and Herzegovina .....
☒ BB Barbados
☒ BG Bulgaria .....
☒ BR Brazil .....
☒ BY Belarus
☒ CA Canada
☒ CH and LI Switzerland and Liechtenstein
☒ CN China .....
☒ CU Cuba .....
☒ CZ Czech Republic .....
☒ DE Germany .....
☒ DK Denmark .....
☒ EE Estonia .....
☒ ES Spain .....
☒ FI Finland .....
☒ GB United Kingdom
☒ GE Georgia .....
☒ GH Ghana .....
☒ GM Gambia
☒ GW Guinea-Bissau .....
☒ HR Croatia
☒ HU Hungary .....
☒ ID Indonesia
☒ IL Israel .....
☒ IS Iceland
☒ JP Japan .....
☒ KE Kenya .....
☒ KG Kyrgyzstan .....
☒ KP Democratic People's Republic of Korea .....
☒ KR Republic of Korea .....
☒ KZ Kazakhstan .....
☒ LC Saint Lucia
☒ LK Sri Lanka
☒ LR Liberia
☒ LS Lesotho .....
☒ LT Lithuania
☒ LU Luxembourg
☒ LV Latvia
☒ MD Republic of Moldova .....
☒ MG Madagascar .....
☒ MK The former Yugoslav Republic of Macedonia .....
☒ MN Mongolia
☒ MW Malawi .....
☒ MX Mexico .....
☒ NO Norway
☒ NZ New Zealand .....
☒ PL Poland .....
☒ PT Portugal .....
☒ RO Romania
☒ RU Russian Federation .....
☒ SD Sudan
☒ SE Sweden
☒ SG Singapore
☒ SI Slovenia .....
☒ SK Slovakia .....
☒ SL Sierra Leone
☒ TJ Tajikistan .....
☒ TM Turkmenistan .....
☒ TR Turkey .....
☒ TT Trinidad and Tobago .....
☒ UA Ukraine .....
☒ UG Uganda .....
☒ US United States of America .....
☒ UZ Uzbekistan .....
☒ VN Viet Nam .....
☒ YU Yugoslavia .....
☒ ZW Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

☒ ~~Guatemala~~ .....
☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope f this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration f that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

PATENT COOPERATION TREATY

RECEIVED
OCT 28 1998
Docket Sec.
Vinson & Elkins

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF RECEIPT OF SEARCH COPY

(PCT Rule 25.1)

To:
Vinson & Elkins L.L.P.
Attn. SANZO, M.
2300 First City Tower
1001 Fannin Street
Houston, Texas 77002-6760
UNITED STATES OF AMERICA

Date of mailing (day/month/year) 22/10/1998

Applicant's or agent's file reference
NOV550/58000

IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US 98/ 18284	03/09/1998	04/09/1997

Applicant
NOVONEURON, INC. et al.

1. **Where the International Searching Authority and the Receiving Office are not the same office:**

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

Where the International Searching Authority and the Receiving Office are the same office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

07/10/1998 *(date of receipt).*

2. ☐ The search copy was accompanied by a diskette containing nucleotide and/or amino acid sequence listings.

3. **Time limit for establishment of International Search Report**

The applicant is informed that the time limit for establishing the International Search Report is 3 months from the date of receipt indicated above or 9 months from the priority date, whichever time limit expires later

4. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the Receiving Office.

Name and mailing address of the International Searching Authority
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
ISA/EP

Form PCT/ISA/202 (January 1994)

PATENT COOPERATION TREATY

by fax and post

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
PERRY, Robert Edward et al
GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
LONDON EC2M 7LH
GRANDE BRETAGNE

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	01.12.99
Applicant's or agent's file reference	REPLY DUE within 15 days from the above date of mailing
NOV550/58000	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/18284	03/09/1998	04/09/1997

International Patent Classification (IPC) or both national classification and IPC
A61K31/00

Applicant
NOVONEURON, INC. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 04/01/2000.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
T l. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Smetankine, L

Formalities officer (incl. extension of time limits)
Senkel, H
Telephone No. +49 89 2399 8071

WRITTEN OPINION

International application No. PCT/US98/18284

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-10 as originally filed

Claims, No.:

1-24 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-9,

because:

- ☒ the said international application, or the said claims Nos. 1-9 relate to the following subject matter which does not require an international preliminary examination (*specify*):

  see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☐ all parts.

☒ the parts relating to claims Nos. 1-9.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1,4(part)
Inventive step (IS)	Claims	1,4 (part),5(part),6-9
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/US98/18284

POINT III:

Claims 1-9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

POINT V:

1. Novelty:

BRAIN RESEARCH, vol. 741, n°1-2,1996, pp.258-262 (1) - see abstract, page 259 left - hand column last paragraph to right - hand column paragraph 1, describes the use of noribogaine by systemically administration (40mg/kg of body weight) with morphine to reduce pain, thus claims 1 and 4 (partially) does not seem to be new.

US - A - 3 715 361 (2) - see abstract, column 1 line 60 and column 2 lines 33 and 34, describes the analgesic properties of ibogaine, thus claims 1 to 9 seem to b new.

US - A - 5 426 112 (3) - see claims 1 and 2, which describes the alleviation of pain by opioid antagonist such as naloxone and naltrexone, thus claims 1 to 9 seem to be new.

GB - A - 841 697 (4) - see claims 1-6, page 1 lines 63-85, page 2 lines 51 to 71, describes the analgesic properties of ibogaine, thus claims 1 to 9 seem to be new.

WO - A - 96/03127 (5) - see claim 15, describes the anti - addictive properties of noribogaine, thus claims 1 to 9 seem to be new.

US - A - 5 591 738 (6) - see abstract, claim 1 describes the anti- addictive properties of noribogaine, thus claims 1 to 9 seem to be new.

WRITTEN OPINION
SEPARATE SHEET

International application No. PCT/US98/18284

2. Inventive step:

Concerning claims 1,4(part.) and 5(part.): For a skilled person it is obvious to use 40mg/kg of body weight instead the 30mg/kg of body weight of noribogaine specified in (1): see the above point 1).

Concerning claims 2,3,4(part.) and 5 (partially), the closest document is (1), which describes the analgesic properties of noribogaine when used together with opioid analgesics. In the abstract it is specified that when noribogaine is used alone without morphine, it has no effect. Therefore it was a prejudice for a skilled person to use noribogaine as the sole analgesic agent or in the absence of any concomitant opioid analgesic therapy, therefore these claims seem to be inventive.

Concerning claims 6 to 9: (1) teaches the potentiation of analgesic properties of noribogaine when it is combined with other analgesics. Therefore a skilled person which is aware of the analgesic properties of naloxone and naltrexone by (3) would combine these products with noribogaine in view of (1), thus claims 6 to 9 seem to lack inventive step.

3. Therapeutical treatment:

For the assessment of the present claims 1 to 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREA

From the
INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY

To:

PERRY, Robert Edward et al
GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
LONDON EC2M 7LH
GRANDE BRETAGNE

DIARIED

PCT

INVITATION TO RESTRICT OR TO PAY ADDITIONAL FEES

(PCT Article 34(3) (a) and Rule 68.2)

Date of mailing *(Day/month/year)*	04.08.99
Applicant's or agent's file reference: NOV550/58000	**REPLY OR PAYMENT DUE** within 1 month(s) from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/18284	03/09/1998	04/09/1997

International Patent classification (IPC) or national Patent classification:
A61K31/00

Applicant
NOVONEURON, INC. et al.

1. This International Examining Authority

   (i) considers that **the international application does not comply with the requirements of unity of invention** (Rule 13.1, 13.2 and 13.3) for the reasons indicated in the Annex.

   (ii) therefore considers that there are **3 inventions** claimed in the international application as indicated in the Annex.

   (iii) recalls that claims relating to inventions in respect of which no international search report has been established need not be the subject of international preliminary examination (Rule 66.1 (e)).

2. Consequently the applicant is hereby **invited**, within the time limit indicated above, **to restrict the claims** as suggested under item 3, below, **or to pay** the amount indicated below:

   EUR 1533 (Fee per additional invention) x 02 (number of additional inventions) = EUR 3066 (total amount of additional fees)

   The applicant is informed that, according to Rule 68.3 (c), **the payment of any additional fee may be mad under protest**, i.e. a reasonned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. **If the applicant opts to restrict the claims**, this Authority suggests the restriction possibilities indicated in the Annex, which in its opinion would be in compliance with the requirement of unity of invention.

4. **In the absence of any response** from the applicant, this Authority will establish the international preliminary examination report on those parts of the international application indicated in the Annex which, in the opinion of this Authority appear to relate to the main invention.

Name and mailing adress of the international preliminary examination authority:
European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0 Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer
Tzschoppe, D
C. Sleex

Telephone No. (+49-89) 2399- 873

Form PCT/IPEA/405 (July 1992)

INVITATION TO RESTRICT OR TO PAY ADDITIONAL FEES

International application No. PCT/US98/18284

The present application claims 2 clearly different therapeutic uses for noribogaine (the treatment of pain and the treatment of drug dependence or abuse) and compositions comprising noribogaine and an opioid antagonist. The only common link between these different therapeutic uses and the composition is the fact that noribogaine is involved as the common technical feature. As noribogaine is known as such, this feature cannot form a common inventive concept as it makes no contribution over the prior art.

MASR

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

RECEIVED
JUN 7 1999
Docket Sec.
Vinson & Elkins

SANZO, Michael, A.
Vinson & Elkins
2300 First City Tower
1001 Fannin
Houston, TX 77002-6760
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 31 May 1999 (31.05.99)	
Applicant's or agent's file reference NOV550/58000 4-1(A)	**IMPORTANT INFORMATION**
International application No. PCT/US98/18284	**International filing date** (day/month/year) 03 September 1998 (03.09.98)
Priority date (day/month/year) 04 September 1997 (04.09.97)	
Applicant NOVONEURON, INC. et al	

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,GB,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AL,AM,AT,AZ,BA,BB,BY,CH,CU,DK,EE,ES,FI,GE,GH,GM,HR,HU,ID,IS,KE,
   KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,TJ,TM,TR,TT,UA,
   UG,UZ,VN,YU,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

F. Baechler

Telephone No. (41-22) 338.83.38

2644555

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: REP06002EP

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US98/18284	03 September 1998 (03.09.98)	04 September 1997 (04.09.97)

Title of invention
NORIBOGAINE IN THE TREATMENT OF PAIN AND DRUG ADDICTION

Box No. II APPLICANT(S)

Name and address:
NovoNeuron, Inc.
1 Northeast 19th Street
Suite 399
Miami
Florida 33132
United States America

Telephone No.:

Facsimile No.:

Teleprinter No.:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

Name and address:
MASH, Deborah C
7552 W. Treasure Drive
North Bay Village
Florida 33141
United States of America

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

Name and address:

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US98/18284

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [ ] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[X] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address:

PERRY, Robert Edward
Gill Jennings & Every
Broadgate House
7 Eldon Street
London
EC2M 7LH
United Kingdom

Telephone No.: +44 171 377 1377

Facsimile No.: +44 171 377 1310

Teleprinter No.:

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

[X] the international application as originally filed

the description
[ ] as originally filed
[ ] as amended under Article 34

the claims
[ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings
[ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

[X] which is the language in which the international application was filed.

[ ] which is the language of a translation furnished for the purposes of international search.

[ ] which is the language of publication of the international application.

[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No.V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

International application No.
PCT/US98/18284

Box No.VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ nucleotide and/or amino acid sequence listing in computer readable form
6. ☐ other *(specify)*:

Box No.VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

For the Applicant
Gill Jennings & Every

PERRY, Robert Edward

Date: 18th March 1999

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

WO 99/11250
PCT/US98/18284

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
SANZO, Michael, A.
Vinson & Elkins
2300 First City Tower
1001 Fannin
Houston, TX 77002-6760
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 11 March 1999 (11.03.99)	
Applicant's or agent's file reference NOV550/58000 4-1(A)	**IMPORTANT NOTICE**
International application No. PCT/US98/18284	**International filing date** (day/month/year) 03 September 1998 (03.09.98)
Priority date (day/month/year) 04 September 1997 (04.09.97)	
Applicant NOVONEURON, INC. et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BR,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GE,GH,GM,HR,HU,ID,IS,
   KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,
   SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   11 March 1999 (11.03.99) under No. WO 99/11250

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/308 (July 1996)

2508618

TENT COOPERATION TREATY

PCT

Fr m th INTERNATIONAL SEARCHING AUTHORITY

To:
Vinson & Elkins L.L.P.
Attn. SANZO, M.
2300 First City Tower
1001 Fannin Street
Houston, Texas 77002-6760
UNITED STATES OF AMERICA

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

Applicant's or agent's file reference NOV550/58000	Date of mailing *(day/month/year)* 10/03/1999
International application No. PCT/US 98/ 18284	**PAYMENT DUE** within 45 ~~months~~/days from the above date of mailing
	International filing date *(day/month/year)* 03/09/1998
Applicant NOVONEURON, INC. et al.	

1. This International Searching Authority

(i) considers that there are 3 *(number of)* inventions claimed in the international application covered by the claims indicated ~~below~~/on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~/on the extra sheet:

(ii) [X] has carried out a partial international search (see Annex) [ ] will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:
1 - 9

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited,** within the time limit indicated above, to pay the amount indicated below:

DEM 2 198,35 (Fee per additional invention) x 2 (number of additional inventions) = DEM 4 396,70 (total amount of additional fees)

Or, EUR 1 124, - x 2 = EUR 20248, -

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest,** i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. [ ] Claim(s) Nos. _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Véronique Bailliou

Form PCT/ISA/206 (July 1992)

EINSCHREIBEN

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/US 98/18284

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-9

   Method of treating pain comprising administering noribogaine

2. Claims: 10-18

   Method of treating drug dependence or abuse during withdrawal therapy involving administration of noribogaine

3. Claims: 19-24

   Compositions containing noribogaine and a opioid antagonist

The present application claims 2 clearly different therapeutic uses for noribogaine and compositions comprising noribogaine and an opioid antagonist. The only common link between these different therapeutic uses and the composition is the fact, that noribogaine is involved. As noribogaine is known as such this link cannot form a common inventive concept, since it is already known and thus makes no contribution over the prior art. A complete search would necessitate a further substantial search effort.

Anne[illegible]rm PCT/ISA/206
COMMUNICATIO[illegible]ELATING TO THE RESULTS OF THE PARTIAL INTERNATIONAL SEARCH

[illegible]tional Application No
PCT/US 98/18284

1. Th present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
1-9
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.

3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.

4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	A.A.BAGAL ET AL.: "Modulation of morphine-induced antinociception by ibogaine and noribogaine" BRAIN RESEARCH, vol. 741, no. 1-2, 1996, pages 258-262, XP002094531 see abstract	1-9
Y	US 3 715 361 A (J.W.EPSTEIN ET AL.) 6 February 1973 see column 1 - column 2	1-9
Y	US 5 426 112 A (IAN S. ZAGON ET AL.) 20 June 1995 see claims 1,2	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

[redacted]ent Family Annex

Information on patent family members

[redacted]tional Application No
PCT/US 98/18284

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3715361 A	06-02-1973	NONE	
US 5426112 A	20-06-1995	US 5266574 A	30-11-1993
		US 4689332 A	25-08-1993
		CA 1228814 A	03-11-1987
		JP 1855454 C	07-07-1994
		JP 60218320 A	01-11-1985

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PERRY, Robert Edward et al
GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
LONDON EC2M 7LH
GRANDE BRETAGNE

RECEIVED
28 JAN 2000
GILL JENNINGS & EVERY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 25.01.2000
Applicant's or agent's file reference NOV550/58000	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/18284	03/09/1998	04/09/1997

Applicant
NOVONEURON, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Senkel, H Tel.+49 89 2399-2362

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
NOV550/58000		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/18284	03/09/1998	04/09/1997
International Patent Classification (IPC) or national classification and IPC		
A61K31/00		
Applicant		
NOVONEURON, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19/03/1999	25.01.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Smetankine, L Telephone No. +49 89 2399 8466

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/18284

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-10 as originally filed

Claims, No.:

1-24 as originally filed

Drawings, sheets:

1/1 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-18.

because:

☒ the said international application, or the said claims Nos. 1-18 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,3,4(part),5(part),6-9,20-24
	No:	Claims	1,4(part),10-17,19
Inventive step (IS)	Yes:	Claims	2,3,4(part),5(part)
	No:	Claims	1,4 (part),5(part),6-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

see separate sheet

POINT III:

Claims 1-9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

POINT IV:

The present application claims two different therapeutic uses of noribogaine (the treatment of pain and the treatment of drug dependence or abuse) and compositions containing noribogaine and an opioid antagonist. The only common link between these different therapeutic uses and the compositions is the fact that noribogaine is involved as the common technical feature. As noribogaine is known as such and as medicament, this feature cannot form a common inventive concept as it makes no contribution over the prior art.

Therefore this application contains three inventions as follows:

1. Claims 1-9: the method of treating pain by administration of noribogaine.

2. Claims 10 to 18: the method of treating drug dependence or abuse during withdrawal therapy involving administration of noribogaine.

3. Claims 19 to 24: compositions containing noribogaine and opioid antagonist.

The lack of unity would be objected as explained above when the application will be examined in a national or regional way.

POINT V:

1. Novelty:

BRAIN RESEARCH, vol. 741, n°1-2,1996, pp.258-262 (1) - see abstract, page 259 left - hand column last paragraph to right - hand column paragraph 1, describes the use of noribogaine by systemically administration (40mg/kg of body weight) with morphine to reduce pain, and also the anti- addictive effect of noribogaine. Further (1) discloses the treatment of addiction to a narcotic such as morphine, thus claims 1 ,4(part), 10,11,13 does not seem to be new.

US - A - 3 715 361 (2) - see abstract, column 1 line 60 and column 2 lines 33 and 34, describes the analgesic properties of ibogaine, thus claims 1 to 24 seem to be new.

US - A - 5 426 112 (3) - see claims 1 and 2, which describes the alleviation of pain by opioid antagonist such as naloxone and naltrexone, thus claims 1 to 24 seem to be new.

GB - A - 841 697 (4) - see claims 1-6, page 1 lines 63-85, page 2 lines 51 to 71, describes the analgesic properties of ibogaine, thus claims 1 to 24 seem to be new.

WO - A - 96/03127 (5) - see page 9 lines 2 to 5, claims 1 to 18, describes the anti - addictive properties of noribogaine, used at a dosage of 0.01 to 100mg per kg of body weight for the treatment of drug dependence or abuse during withdrawal therapy to reduce symptoms of drug withdrawal, wherein the drug is a narcotic such as cocain, heroin, alcohol, methadone, amphetamine, thus claims 10 to 17 seem to be not new.

US - A - 5 591 738 (6) - see abstract, column 6 line 25 to column 7 line 44,

claim 1 describes the anti- addictive properties of noribogaine, when it is used for the treatment of drug dependency (wherein the dependency drug is heroin, methadone, cocaine,alcohol, amphetamine) or abuse during withdrawal therapy by noribogaine administration. Pharmaceutical compositions comprising noribogaine and opioid antagonist are also disclosed. Therefore claims 10 to 12,15,19 and 20 seem to lack novelty.

2. Inventive step:

Concerning claims 1,4(part.) and 5(part.): For a skilled person and in view of the disclosure in (1), it is obvious to use 40mg/kg of body weight instead the 30mg/kg of body weight of noribogaine specified in (1): see the above point 1).

Concerning claims 2,3,4(part.) and 5 (partially), the closest document is (1), which describes the analgesic properties of noribogaine when used together with opioid analgesics. In the abstract it is specified that when noribogaine is used alone without morphine, it has no effect. Therefore it was a prejudice for a skilled person to use noribogaine as the sole analgesic agent or in the absence of any concomitant opioid analgesic therapy, therefore these claims seem to be inventive.

Concerning claims 6 to 9: (1) teaches the potentiation of analgesic properties of noribogaine when it is combined with other analgesics. Therefore a skilled person which is aware of the analgesic properties of naloxone and naltrexone by (3) would combine these products with noribogaine in view of (1), thus claims 6 to 8 and 19 to 23 seem to lack inventive step. Concerning claims 9,18 and 24, the transdermal administration of a therapeutic composition belongs to a matter of routine for a skilled person.

Concerning claims 10 to 18, its subject- matter could be deduced from the

combination of(5) or (6) with (1), this last teaching the amounts of noribogaine to be used or the combination of (5) or (6) with (3), the last teaching the amounts of opioid antagonist to be used, thus claims 1 to 18 seem to lack inventive step.

3. Therapeutical treatment:

For the assessment of the present claims 1 to 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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(71) Applicant *(for all designated States except US)*: NOVONEURON, INC. [US/US]; Suite 399, 1 Northeast 19th Street, Miami, FL 33132 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: MASH, Deborah, C. [US/US]; 7552 W. Treasure Drive, North Bay Village, FL 33141 (US).

(74) Agent: SANZO, Michael, A.; Vinson & Elkins, 2300 First City Tower, 1001 Fannin, Houston, TX 77002–6760 (US).

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(54) Title: NORIBOGAINE IN THE TREATMENT OF PAIN AND DRUG ADDICTION

(57) Abstract

The present invention is directed to methods of treating patients for pain by administering noribogaine. Noribogaine may also be used to treat patients for the symptoms associated with withdrawal from drug dependency. In the latter case, the noribogaine treatment should be supplemented with the administration of an opioid antagonist such as naloxone.

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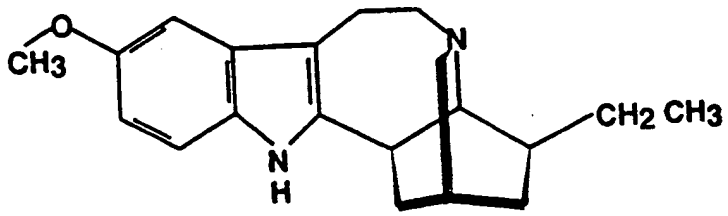
Noribogaine in the Treatment of Pain and Drug Addiction

Field of the Invention

The present invention is concerned with novel pharmaceutical compositions and novel treatment methods. In particular, the invention relates to novel methods for providing analgesia and to novel pharmaceutical compositions containing the drug noribogaine. The compositions particularly include those containing, in addition to noribogaine, one or more opioid antagonists. In addition, the present invention provides novel compositions and methods useful in treating patients for the symptoms associated with withdrawal from drug dependency or abuse.

Background of the Invention

Ibogaine is an indole alkaloid derived from *Tabernanth iboga*, a shrub of West Africa, and is used by indigenous people of that region in religious rituals. The structure of ibogaine has been determined and procedures for its synthesis have been reported (see, Buchi, *et al., J. Am. Chem. Soc. 88*:3099 (1966); Rosenmund, *et al., Chem. Ber. 108*:1871 (1975); and Huffman, *et al., J. Org. Chem. 50*:1460 (1985)). The chemical structure is as follows:



In 1956 Salmoiraghi and Page elucidated ibogaine's relationship to serotonin *(J. Pharm. and Exp. Ther. 120*(1):20-25 (1957)). About the same time Schneider published three important papers: "Potentiation Action of Ibogaine on Morphine Analgesia" (*Experiential 12*:323-24 (1956)); "Neuropharmacological Studies of Ibogaine: An Indole Alkaloid with Central Stimulant Properties ," *(Ann. of N.Y. Acad. Sci. 66*:765-76 (1957)); and "An Analysis of the Cardiovascular Action of Ibogaine HCl," (*Arch. Int. Pharmacodyn. 110*:92-102 (1957)). Dhahir published a review of the pharmacology and toxicology of ibogaine in his doctoral thesis, "A Comparative Study of the Toxicity of Ibogaine and Serotonin" (University

Microfilms International 71-25-341, Ann Arbor, Mich.). The thesis gives an overview of much of the work accomplished with ibogaine.

Additional studies of interest include: "The Effects of Some Hallucinogens on Aggressiveness of Mice and Rats " (Kostowski, *et al.*, *Pharmacology 7*:259-63 (1972)), "Cerebral Pharmacokinetics of Tremor-Producing Harmala and Iboga Alkaloids" (Zetler, *et al.*, *Pharmacology 7(4)*:237-248 (1972)), "High Affinity ^{3}H-Serotonin Binding to Caudate: Inhibition by Hallucinogenic and Serotonergic Drugs" (Whitaker, *et al., Psychopharmacology 59*:1-5 (1978)); "Selective Labeling Of Serotonin Receptors by d-(^{3}H)Lysergic Acid Diethylamide in Calf Caudate" (*Proc. Natl. Acad. Sci., U.S.A. 75(12)*:5783-87 (1978)); and "A Common Mechanism of Lysergic Acid, Indolealkylamine and Phenethylamine Hallucinogens: Serotonergic Mediation of Behavioral Effects in Rats" (Sloviter, *et al., J. Pharm. Exp. Ther. 214(2)*:231-38 (1980)). More current work has been reported by Dzoljic, *et al.*, "Effect of Ibogaine on Naloxone-Precipitated Withdrawal Syndrome in Chronic Morphine Dependent Rats," (*Arch. Int. Pharmacodyn., 294*:64-70 (1988)).

Ibogaine administration has been reported to reduce the withdrawal symptoms associated with drug dependency and to alleviate drug cravings in addicts. It has been disclosed to be effective in the treatment of dependencies resulting from a wide range of drugs, including narcotics (U.S. 4,499,096); cocaine and amphetamines (U.S. 4,587,243); alcohol (U.S. 4,857,523); and nicotine/tobacco (5,026,697). In addition it has been reported to be effective in patients addicted to multiple drugs and drug combinations (5,152,994). Among the specific drug dependencies reportedly amenable to ibogaine treatment are heroin, cocaine, alcohol, nicotine, caffeine, amphetamine, desoxyephedrine, methadone and combinations thereof.

Other pharmacological agents that have been used in the treatment of certain types of drug addiction or dependency include naloxone and naltrexone. However, these agents typically fail to alleviate the often severe suffering that accompanies the drug withdrawal process and are generally ineffective in treating polydrug abuse or addiction. Thus, the prior art has failed to provide a completely satisfactory therapy for drug addiction or abuse and new agents and methods are clearly needed.

Summary of the Invention

In accordance with the present invention, surprising and unexpected properties of noribogaine have been discovered. This compound is known to be a metabolite of ibogaine and is chemically identified as 12-hydroxyibogamine. In particular, noribogaine has been found to be useful as a non-addictive analgesic agent and as a treatment for drug dependency or abuse. Pharmaceutical compositions of noribogaine can be combined with one or more known opioid antagonists to treat addiction such that withdrawal symptoms are substantially eliminated or, at a minimum, surprisingly reduced. Such compositions are conveniently prepared in unit dose form with one or more unit doses providing a therapeutically effective amount of active ingredient.

In its first aspect, the invention is directed to a method of alleviating pain in a patient by administering systemically noribogaine at a therapeutically effective dosage. In a preferred embodiment, administration is by means of a pharmaceutical composition in which noribogaine is the sole analgesic agent. In patients for whom opioid analgesics are contraindicated, noribogaine is administered systemically in an amount of effective to reduce or eliminate pain in the absence of any concomitant opioid analgesic therapy. In each case, the dosage of noribogaine administered to a patient should be between 0.1 and 100 mg per kg of body weight and, preferably, between 1 and 30 mg per kg of body weight.

The present invention also includes a method of treating a patient to alleviate pain by administering systemically noribogaine and one or more opioid antagonists, such that the respective amounts of noribogaine and antagonist are effective to reduce or eliminate pain. If desired, one or more opioid antagonists may also be administered to patients, with the preferred antagonist being naloxone, naltrexone or nalorphine, preferably at a concentration of between 0.15 mg and 0.5 mg for each mg of noribogaine administered. Although, the method is compatible with any route of administration, the transdermal route will generally be the most convenient.

The invention is also directed to a method for treating drug addiction (involving drug dependency or drug abuse) during withdrawal therapy by administering noribogaine to a patient at a dosage sufficient to reduce or eliminate one or more symptoms associated with withdrawal.

Such symptoms include nausea, vomiting, anxiety, abdominal cramps, muscle pain, chills and headache. In addition, noribogaine treatment decreases the drug cravings normally experienced by addicts after cessation of the self administration of the abused substance. Noribogaine is especially useful in the treatment of addiction to narcotics such as heroin and methadone. However, it is also useful in treating patients addicted to cocaine, alcohol, amphetamines and combinations of these drugs. It is preferred that the noribogaine be administered to patients suffering from drug dependance or abuse in conjunction with an opioid antagonist such as naloxone, naltrexone or nalorphine. The dosage of noribogaine should be as discussed above in conjunction with its use in the alleviation of pain. Again, the transdermal route of administration is generally preferred.

In addition to the methods discussed above, the present invention is directed to a pharmaceutical composition, preferably in unit dose form, comprising noribogaine and one or more opioid antagonists. When administered to a patient, one or more unit doses provide an amount of noribogaine and of opioid antagonist effective to treat drug dependency or to provide analgesia. Noribogaine should generally be present in such compositions at a concentration of between about 0.1 and 20 mg/ml. When either naloxone or naltrexone is used as an opioid antagonist in compositions, they should be present at 0.05 to 0.5 mg for each mg of noribogaine.

The present invention contemplates that the administration of active ingredients will be accomplished by any systemic route which is convenient and readily accessible to the attending physician. While all of the various conventional routes of administration are contemplated (*e.g.*, transdermal, intranasal, intramuscular, subcutaneous, intravenous, vaginal, rectal, buccal and oral), the preferred route of administration is transdermally.

The present invention further contemplates the use of noribogaine as an adjunct to conventional drug withdrawal therapy, specifically providing for the administration of noribogaine concomitantly with one or more opioid antagonists. "Concomitant"administration refers to the administration of the two agents (*i.e.*, noribogaine and an opioid antagonist) in any manner in which the pharmacological effects of both are manifest in the patient at the same time. Thus, concomitant administration does not require that a single pharmaceutical

composition, the same dosage form, or even the same route of administration be used for administration of both noribogaine and opioid antagonist or that the two agents be administered at precisely the same time. However, concomitant administration will be accomplished most conveniently by the same dosage form and the same route of administration, at substantially the same time. Obviously, such administration most advantageously proceeds by delivering both active ingredients simultaneously in a novel pharmaceutical composition in accordance with the present invention.

Pharmaceutical compositions in accordance with the invention are prepared by conventional means using methods known in the art. For example, there are known in the art methods for the preparation of opioid antagonist pharmaceutical compositions fully adaptable to the preparation of compositions of both noribogaine and opioid antagonists. Solid pharmaceutical compositions are provided in accordance with the present invention in unit dosage form. A unit dosage for a solid pharmaceutical composition refers to the amount of each of the active ingredients which is administered in any one entity. Thus, the unit dosage form of a solid pharmaceutical composition makes reference to a discreet entity (*e.g.*, a capsule, tablet, suppository, or drug-releasing device), one or more of which entities contains an appropriate dosage for a single administration.

Accordingly, solid pharmaceutical compositions in accordance with the invention are adaptable to provide administration by transdermal, intranasal, oral, vaginal, rectal, and buccal routes. However, for parenteral routes (*e.g.*, subcutaneous, intravenous, and intraarterial) novel liquid pharmaceutical compositions in accordance with the present invention are provided. Also provided are novel liquid pharmaceutical compositions suitable for oral administration (*e.g.*, syrups and elixirs). Each of these pharmaceutical compositions is prepared by methods known in the art.

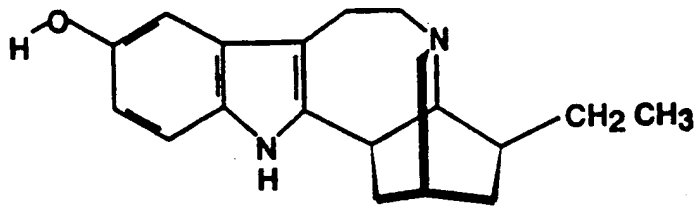
Brief Description of the Figures

Figure 1 (panels A and B): Panel A shows the stimulation of [^{35}S]GTPγS binding to rat thalamic membranes by various concentrations of noribogaine (■) and ibogaine ( ). Results are expressed as percent maximal stimulation (defined by 10 μM DAMGO). Panel B shows the inhibitory shift of noribogaine-stimulated [^{35}S]GTPγS binding by naloxone (0.1 μM).

Detailed Description of the Invention

Noribogaine, a metabolite of ibogaine, has properties that are well suited to the treatment of pain and to the withdrawal symptoms associated with drug dependency or abuse. In particular, it has been discovered that noribogaine binds to two classes of opioid receptors that have been associated with pain relief, the μ and κ receptors. In the case of the μ-type receptors, it appears that noribogaine acts as a full opiate agonist. In addition, noribogaine elevates brain serotonin levels by blocking synaptic reuptake. It is believed that such levels (as well as ligand interactions at the μ and κ opiate receptors) play a role in the anxiety and drug cravings experienced by addicts during withdrawal.

Noribogaine is synthesized by the O-demethylation of ibogaine. This may be accomplished, for example, by reacting ibogaine with boron tribromide/methylene chloride at room temperature and then purifying the product using known procedures. At present, noribogaine may also be obtained from the National Institute on Drug Abuse (Rockville, MD). The compound has the following structure:



Chemical Form of Noribogaine

The present invention is not limited to any particular chemical form of noribogaine and the drug may be given to patients either as a free base or as a pharmaceutically acceptable acid addition salt. In the latter case, the hydrochloride salt is generally preferred, but other salts derived from organic or inorganic acids may also be used. Examples of such acids include, without limitation, hydrobromic acid, phosphoric acid, sulfuric acid, methane sulfonic acid, phosphorous acid, nitric acid, perchloric acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, aconitic acid, salicylic acid, thalic acid, embonic acid, enanthic acid, and the like. As discussed above, noribogaine itself may be formed by the O-demethylation of ibogaine which, in turn, may be synthesized by methods known in the art (*see e.g.*, Huffman, *et al.*, *J.Org. Chem. 50*:1460 (1985)).

Preferred Dosage Forms and Route of Administration

As noted above, any route of administration and dosage form is compatible with the treatments discussed above and noribogaine may be administered as either the sole active agent or in combination with other therapeutically active drugs. In this regard, it is preferred that pharmaceutical compositions, especially those used in the treatment of drug addiction or abuse, contain one or more opioid antagonists. Although compositions suitable for oral delivery will probably be used most frequently, other routes that may be used include peroral, internal, pulmonary, rectal, nasal, vaginal, lingual, intravenous, intraarterial, intramuscular, intraperitoneal, intracutaneous and subcutaneous routes. Especially preferred is the transdermal route of delivery in which drug is applied as part of a cream, gel or, preferably, patch (for examples of transdermal formulations, see U.S. 4,806,341; 5,149,538; and 4,626,539). Other dosage forms include tablets, capsules, pills, powders, aerosols, suppositories, parenterals, and oral liquids, including suspensions, solutions and emulsions. Sustained release dosage forms may also be used. All dosage forms may be prepared using methods that are standard in the art (*see e.g.*, Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton PA 1980)).

Noribogaine is preferably used in conjunction with any of the vehicles and excipients commonly employed in pharmaceutical preparations, *e.g.*, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous solvents, oils, paraffin derivatives, glycols, etc. Coloring and flavoring agents may also be added to preparations, particularly to those for oral administration. Solutions can be prepared using water or physiologically compatible organic solvents such as ethanol, 1,2-propylene glycol, polyglycols, dimethylsulfoxide, fatty alcohols, triglycerides, partial esters of glycerine and the like. Parenteral compositions containing noribogaine may be prepared using conventional techniques that may include sterile isotonic saline, water, 1,3-butanediol, ethanol, 1,2-propylene glycol, polyglycols mixed with water, Ringer's solution, etc.

When formulating compositions containing noribogaine in combination with an opioid antagonist, the preferred antagonist will be naloxone, naltrexone or nalorphine. These agents are commercially available and have been approved for the treatment of opioid withdrawal. In general, noribogaine or a pharmaceutically acceptable salt of noribogaine should be present in the pharmaceutical compositions at a concentration of between 0.1 and 20 mg/ml. Naloxone,

naltrexone, or nalorphine should preferably be present at about 0.05 to about 0.5 mg for each mg of noribogaine. The antagonist may be added in any chemical form which is stable in the particular formulation being prepared.

Method of Treatment

Patients will be administered noribogaine or a composition containing noribogaine together with opioid antagonist, either for the treatment of pain or for the treatment of drug dependency or abuse. In either case, dosage will be selected to reduce or eliminate one or more of the symptoms experienced by the patient. Thus, when noribogaine is being administered as an analgesic, sufficient drug should be given to reduce or eliminate the patient's pain. In the case of drug withdrawal, noribogaine should be given at a dosage sufficient to reduce symptoms commonly associated this process, for example, headache and muscular pain, and preferably at a dosage sufficient to also reduce drug cravings. For both treatments, daily dosage will typically be between 0.1 mg and 100 mg of noribogaine per kg of patient body weight and preferably between 1 mg and 30 per kg of patient body weight. Dosage may be provided in single or divided doses. These dosages are simply guidelines and the actual dose selected for an individual patient will be determined by the attending physician based upon clinical conditions and using methods well known in the art. Compositions may be provided in either a single or multiple dosage regimen, (*e.g.*, a patient may take 3 mg of a noribogaine composition orally three times a day). Alternatively, drug may be administered in an essentially continuous manner using a transdermal preparation or patch.

When noribogaine is used in the treatment of pain, administration may be required on a long term basis and the drug may be taken in a prescribed regimen (as discussed above) or as needed by the patient. Long term treatment may also be necessary in the treating patients for drug dependency or abuse. Sustained release dosage forms or transdermal patches are generally preferred in treating these patents.

Advantages

One of the main advantages of noribogaine is that it is not habit forming. Thus, pain relief can be accomplished without the risk of dependence associated with the chronic use of narcotics. Similarly, patients treated for drug dependence or abuse may be given noribogaine

without the abuse/dependence problems presented by treatment with agents such as methadone. In fact, patients participating in drug substitution programs may want to use noribogaine to taper off the substitute. Also, by alleviating some of the worst aspects of the drug withdrawal process, noribogaine should be a form of therapy that poeple dependent upon, or abusing, drugs will find acceptable.

Examples

Noribogaine-stimulated [^{35}S]GTPγS binding to rat thalamic membranes was used to measure receptor activation of G proteins and results are shown in Figure 1 and Table 1. The percent maximal stimulation (10 μM DAMGO, EC_{50} = 7.4 +/- 0.1 nM) of [^{35}S]GTPγS binding stimulated by noribogaine was determined in the presence of an excess of GDP. The EC_{50} value for noribogaine-stimulated binding was 0.324 +/- 0.015 μM. In contrast, ibogaine caused a weak stimulation of [^{35}S]GTPγS binding even at concentrations above 100 μM. Noribogaine - stimulated binding was blocked in the presence of naloxone (competitive antagonist, EC_{50} = 35 +/- 1.8 μM), demonstrating further that the effect of noribogaine was μ-receptor mediated. The rightward shift of the concentration/effect relationship of noribogaine-stimulated binding with increasing concentration of naloxone was similar to that measured for DAMGO in the presence of competitive antagonist. The level of [^{35}S]GTPγS binding stimulated by noribogaine was in close agreement to the maximal number of [^{35}S]GTPγS binding sites that could be occupied after DAMGO stimulation of G proteins.

Taken together, these results demonstrate that noribogaine acts as a full agonist of the μ-opioid receptor and that it has efficacy as an antinociceptive agent that can used without the abuse liability inherent opiates. Results also indicate that noribogaine may effectively be used, either alone or in conjunction with an opioid antagonist, in the treatment of drug addition.

Table 1: Stimulation of [^{35}S]GTPγS Binding to Rat (Sprague Dawley) Thalamic Membranes by Opioid Agonists of Varying Efficacy

Drug	[^{35}S]GTPγS Binding EC_{50}(nM)
Buprenorphine	0.7 ± 0.1
DAMGO	7.4 ± 0.1
Morphine	52 ± 6.3
Noribogaine	324 ± 15.5
Naloxone	NE
Buprenorphine + Naloxone	301 ± 44
DAMGO + Naloxone	2,230 ± 131
Morphine + Naloxone	26,000 ± 842
Noribogaine + Naloxone	236,000 ± 3,410

Values are means ± S.E. from three or more separate experiments. EC_{50} = concentration of drug producing half maximal stimulation of binding.

All references cited herein are fully incorporated by reference. Having now fully described in the invention, it will be understood by those of skill and the art that the invention may be practiced within a wide and equivalent range of conditions, perimeters and the like without effecting the spirit or scope of the invention or any embodiments thereof.

What is Claimed is:

1. A method of treating a patient to alleviate pain, comprising: administering systemically an amount of noribogaine to said patient effective to reduce or eliminate pain in said patient

2. The method of claim 1, wherein said patient is administered a pharmaceutical composition comprising said noribogaine and wherein said noribogaine is the sole analgesic agent in said pharmaceutical composition.

3. A method of alleviating pain in a patient for whom opioid analgesics are contraindicated, comprising: administering systemically an amount of noribogaine to said patient effective to reduce or eliminate pain in said patient in the absence of any concomitant opioid analgesic therapy.

4. The method of any one of claims 1-3, wherein said noribogaine is administered to said patient at a dose of between 0.1 mg and 100 mg per kg of body weight.

5. The method of claim 4, wherein said noribogaine is administered at a dose of between 1.0 mg and 30 mg per kg of body weight.

6. A method of treating a patient to alleviate pain, comprising:
   a) administering systemically to said patient an amount of noribogaine; and
   b) concomitantly administering systemically to said patient an amount of one or more opioid antagonists;

   wherein said respective amounts of noribogaine and said one or more opioid antagonists are effective to reduce or eliminate pain in said patient.

7. The method of claim 6, wherein said opioid antagonist is naloxone, administered to said patient at a dose of between 0.05 mg and 0.5 mg for each mg of noribogaine.

8. The method of claim 6, wherein said opioid antagonist is naltrexone, administered to said patient at a dose of between 0.05 mg and 0.5 mg for each mg of noribogaine.

9. The method of claim 6, wherein said noribogaine and said opioid antagonist are administered transdermally.

10. A method of treating a patient for drug dependence or abuse during withdrawal therapy which comprises: administering systemically an amount of noribogaine to said patient effective to reduce one or more symptoms of drug withdrawal.

11. The method of claim 10, wherein said patient is treated for addiction to a narcotic.

12. The method of claim 10, wherein said patient is treated for addiction to a drug selected from the group consisting of: cocaine, heroin, alcohol, methadone, amphetamines and combinations thereof.

13. The method of claim 10, wherein said noribogaine is administered at a dose of between 0.1 mg and 100 mg per kg of body weight.

14. The method of claim 13, wherein said noribogaine is administered at a dosage of between 1.0 mg and 30 mg per kg of body weight.

15. The method of claim 10, further comprising administering an opioid antagonist to said patient.

16. The method of claim 15, wherein said opioid antagonist is naloxone, administered to said patient at a dose of between 0.05 mg and 0.5 mg per mg of noribogaine administered to said patient.

17. The method of claim 15, wherein said opioid antagonist is naltrexone administered at a dose of between 0.05 mg and 0.5 mg per mg of noribogaine administered to said patient.

18. The method of claim 15, wherein said noribogaine and said opioid antagonist are administered transdermally.

19. A pharmaceutical composition comprising:
    a) noribogaine; and
    b) one or more opioid antagonists.

20. The pharmaceutical compositon of claim 19, wherein said composition is in unit dose form and wherein one or more of said unit doses provide an amount of said noribogaine and an amount of said one or more opioid antagonists effective to treat drug dependency, or drug abuse, or to produce analgesia in a patient to whom said unit dose or unit doses are administered.

21. The pharmaceutical composition of either claim 19 or claim 20, wherein said noribogaine is present at a concentration of between 0.1 mg/ml and 20 mg/ml.

22. The pharmaceutical composition of either claim 19 or claim 20, wherein said opioid antagonist is naloxone present at 0.05 mg to 0.5 mg for each mg of noribogaine.

23. The pharmaceutical composition of either claim 19 or claim 20, wherein said opioid antagonist is naltrexone present at 0.05 mg to 0.5 mg for each mg of noribogaine.

24. The pharmaceutical composition of either claim 19 or claim 20, wherein said pharmaceutical composition is formulated for transdermal delivery.

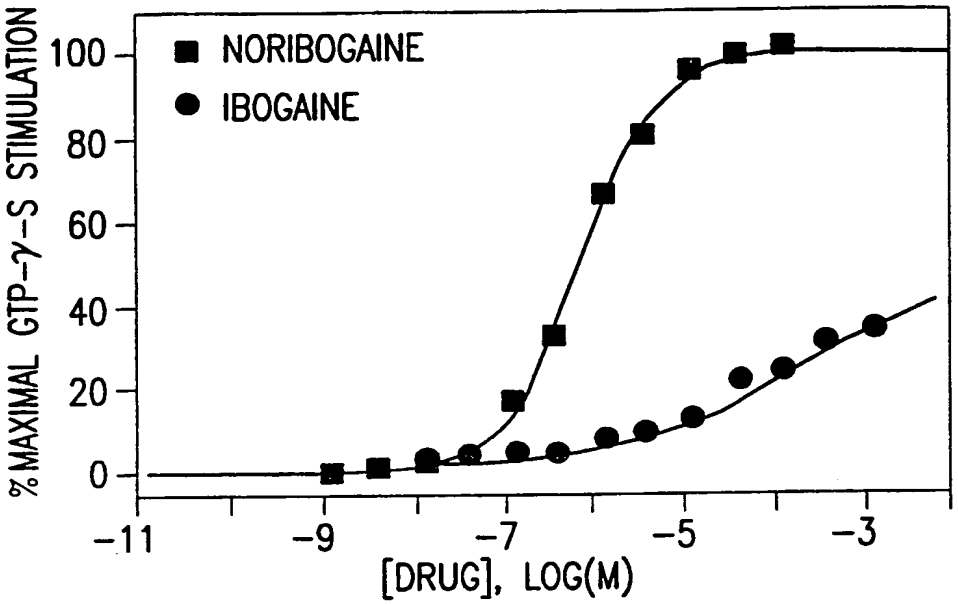

% MAXIMAL GTP-γ-S STIMULATION
100
80
60
40
20
0
NORIBOGAINE
IBOGAINE
-11
-9
-7
-5
-3
[DRUG], LOG(M)

FIG.1A

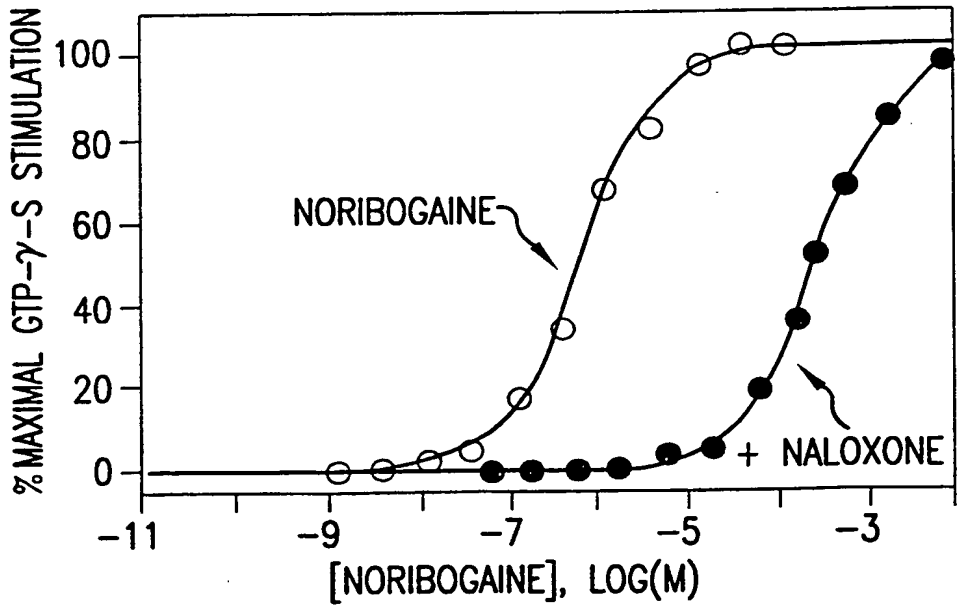

% MAXIMAL GTP-γ-S STIMULATION
100
80
60
40
20
0
NORIBOGAINE
+ NALOXONE
-11
-9
-7
-5
-3
[NORIBOGAINE], LOG(M)

FIG.1B